

Clinical and laboratory factors associated with negative oral food challenges

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ABSTRACT

Children with food-specific IgE (FSIgE) ≤ 2 kUa/L to milk, egg, or peanut (or ≤ 5 kUa/L to peanut without history of previous reaction) are appropriate candidates for oral food challenge (OFC) to investigate resolution of food allergy, because these FSIgE cutoffs are associated with $\sim 50\%$ likelihood of negative OFC. This study was designed to identify characteristics of children undergoing OFC, based on these FSIgE levels, who are most likely to show negative OFC. We collected demographics, severity of previous reaction, history of atopic diseases, total IgE and FSIgE values, and skin tests results on children who underwent OFCs to milk, egg, or peanut, based on the recommended FSIgE cutoffs. We identified independent factors associated with negative OFCs. Four hundred forty-four OFCs met our inclusion criteria. The proportions of negative OFCs performed based on FSIgE cutoffs alone were 58, 42, and 63% to milk, egg, and peanuts, respectively. Regression models identified independent factors associated with negative OFCs: lower FSIgE levels (all three foods), higher total IgE (milk), consumption of baked egg products (egg), and non-Caucasian race (eggs and peanuts). Combinations of these factors identified subgroups of children with proportions of negative OFCs of 83, 75, and 75% for milk, eggs, and peanuts, respectively. Combinations of clinical and laboratory elements, together with FSIgE values, might identify more children who are likely to have negative OFCs compared with current recommendations using FSIgE values alone. Once validated in a different population, these factors might be used for selection of patients who are most likely to show negative OFCs.

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Milk and egg allergy are often considered transient disorders,¹ whereas peanut allergy is considered to be more persistent.² Oral food challenges (OFCs) are the recommended procedure to document the resolution of food allergy,^{3,4} but they are time-consuming, difficult to perform, require resources, and expose the patient to the risk of a significant allergic reaction. Food-specific IgE (FSIgE) levels have been used to predict the outcome of OFC because FSIgE levels above certain cut points were found to be highly predictive of positive OFCs.^{5–10} However, FSIgE levels are less effective in identifying children who experience a negative OFC.¹¹

In clinical practice, children with a known food allergy are considered appropriate candidates for OFCs to evaluate for resolution of food allergy when the likelihood of

a positive OFC is $\leq 50\%$.³ Previous research¹¹ has revealed that FSIgE of ≤ 2 kUa/L (or ≤ 5 kUa/L for peanuts without a history of previous reaction) are associated with an estimated $\leq 50\%$ likelihood of reacting to eggs, milk, or peanuts during an OFC, and these FSIgE values have been incorporated into clinical guidelines.¹¹ Identifying additional clinical and laboratory factors associated with negative OFC within this group of patients would improve patient care by decreasing the number of unnecessary (*i.e.*, predictably positive) OFCs.

Recently, it was shown that the incorporation of clinical and laboratory data to supplement FSIgE levels effectively diagnosed food allergy and might eliminate the need for some OFCs to confirm the presence of food allergy.^{12,13} We extended this approach to the clinical scenario aimed at increasing the accuracy of identifying children who will experience negative OFCs. We aimed to investigate if there are food-specific combinations of clinical and laboratory characteristics that define subgroups of children, undergoing OFC based on the guideline-recommended FSIgE levels,³ who are most likely to experience a negative OFC.

MATERIALS AND METHODS

Study Population

The study population included patients who underwent graded OFC to milk, eggs, and peanuts in the Division of Pediatric Allergy, Immunology, and Pul-

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monary Medicine in Washington University at St. Louis, MO, between August 2004 and July 2010. OFCs were performed to identify children who may have become tolerant to a previously reactive food or to investigate the clinical significance of positive FSIgE in the subgroup of children who had never eaten the food and thus never experienced a clinical reaction to the food (referred to as “sensitization only”). This subgroup of children who had never eaten the food (“sensitization only”) underwent FSIgE and/or skin testing to food from different clinical reasons such as confirmed food allergy to another food, older siblings with food allergy, or as part of evaluation for moderate-severe eczema. If testing was positive, these children were advised to avoid the food and were scheduled for an OFC to investigate whether these positive tests actually represent clinical food allergy, or allergic sensitization without clinical significance. OFCs to these children were performed once their FSIgEs were below the FSIgE values recommended by clinical guidelines.³

A diagnosis of food allergy required a convincing history of immediate reaction after the isolated ingestion of the food and evidence of allergic sensitization to this food (positive skin-prick test and/or FSIgE).¹⁰ OFCs were performed if the level of FSIgE was ≤ 2 kUa/L to milk, eggs, or peanuts (or ≤ 5 kUa/L to peanuts with sensitization only), as recommended by current food allergy guidelines.^{3,11} OFCs were performed at least 6 months after the last clinical reaction to the food. OFC was not performed if a child had allergen ingestion without clinical reaction since his last clinic visit. For the child with multiple OFCs to the same food over time, only the first OFC to that food was included in the analyses. We also excluded from analysis OFCs in which the FSIgE measurements were performed using a method other than Phadia ImmunoCAP system FEIA (Phadia, Uppsala, Sweden).

Oral Challenges

OFC protocols were adopted from Bock *et al.*¹⁴ Briefly, challenges were administered in 11 escalating doses every 15 minutes: egg and peanut challenges were conducted using egg white powder or roasted peanut powder within a carrier up to a maximum of 16.4 g. Milk challenges were conducted using either nonfat milk powder (to a maximum of 16.4 g) or liquid milk (to a maximum of 239 mL). Patients who tolerated the last dose of the graded challenge were observed for an additional 20 minutes. If they did not develop any clinical symptoms of food allergy, then open food challenges were performed to confirm that they could tolerate the food in its usual form and to avoid potential false negative result of the graded challenge.¹⁵ The open challenge consisted of one-half cup of milk, a hard-boiled egg, or peanut butter cracker. Patients

were observed for 2 hours after the open challenge. If they remained asymptomatic after this period, the challenge was considered negative and we recommended routine consumption of the food thereafter. A positive challenge was defined as the presence of objective symptoms (oral, skin, gastrointestinal, respiratory, and/or cardiovascular) noted by the allergist during the challenge.^{3,16} In a case of nonobjective symptoms such as itchiness, abdominal pain, or throat tightness, OFC was temporarily paused until either complete resolution of symptoms or appearance of typical objective symptoms of food allergy. If symptoms promptly resolved spontaneously, then the previous dose was repeated. All patients were observed for 2 hours after completion the OFC to monitor for appearance of potential late reactions.

Data Collection and Statistical Analyses

Patients' demographics, clinical data, and laboratory data are routinely collected before each OFC. We used a structured instrument to extract the relevant data to this study. The Washington University Institutional Review Board approved this study, and a waiver of written consent was granted for retrospective data collection.

For each food, chi-square tests and *t*-tests were used to identify factors that were significantly associated with whether the OFC was positive or negative. Factors that had a value of $p \leq 0.1$ in each of these univariate models were included in stepwise logistic regression analyses. Three separate logistic regression models were developed, one for each food: milk, eggs, and peanuts. The area under each receiver operating characteristic (ROC) curve was generated and the cut point for optimal sensitivity and specificity values was identified for each food. Undetectable FSIgEs (<0.35 kUa/L) were assigned a value of 0.175 kUa/L because this was the median point of the 0- to 0.35-kUa/L range.

Finally, to apply the results from our model to the clinical practice, we aimed to identify subgroups of children who were more likely to have negative OFCs. We categorized significant continuous predictors (FSIgE and total IgE) using tertiles or median splits and combined these with significant categorical predictors. Tertile splits were used for egg and peanut FSIgEs, whereas median splits were used for milk FSIgE because of the smaller sample size. This resulted in subgroups that represent all potential combinations of significant predictors for negative OFCs. We calculated the proportion of negative OFCs in each one of these combinations. All analyses were performed using SAS Version 9.2 (SAS Institute, Inc., Cary, NC). For all analyses, values of $p \leq 0.05$ were considered statistically significant.

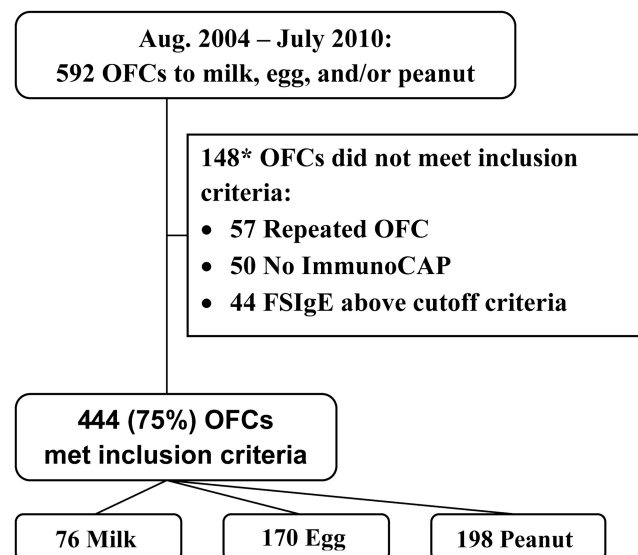


Figure 1. Flow of data collection. *Three OFCs were excluded based on more than one criteria. OFC, oral food challenge; FSIgE, food-specific IgE.

RESULTS

Study Population Characteristics

Of the 592 graded OFCs performed in our clinic between August 2004 and July 2010, 444 (75%) met inclusion criteria and were included in our analyses (Fig. 1). Of these 444 OFCs, 76 were to milk, 170 to egg, and 198 to peanut. The majority of the patients were boys (66%) and Caucasian (76%), with a mean (SD) age of 58 (32) months at the time of OFC. One hundred twenty-one OFCs (27%) were done in children without history of clinical adverse reaction to the food (*i.e.*, sensitization only). However, the absence of a previous clinical adverse reaction was not associated with the OFC outcome, because the likelihood of having negative OFC was not different between children who had sensitization only and children with history of clinical adverse reaction to the food (Table 1).

The Proportion of Negative OFCs and Univariate Factors Associated with Negative OFCs

Negative OFCs occurred with 58% of milk OFCs, 42% of egg OFCs, and 63% of peanut OFCs. Thirty patients who passed the initial graded challenge developed symptoms during the open challenge: 4, 9, and 17 for milk, eggs, and peanuts, respectively. These numbers represent 5.3, 5.3, and 8.6% of the OFCs to these foods. Univariate analyses identified several factors associated with negative OFCs (Table 1). Mean FSIgE values were significantly lower among children who had negative OFCs to milk ($p = 0.03$) and eggs ($p < 0.01$) compared with children who had positive challenges to these foods, while the mean FSIgE for peanuts did not differ significantly between children with

positive and negative challenges ($p = 0.07$). Children who had negative OFCs to milk had higher total IgE ($p = 0.02$) than those with positive OFCs (Table 1). Non-Caucasian race ($p = 0.01$), history of eating eggs as ingredient in baked goods ($p < 0.01$), and a negative skin test result to eggs ($p < 0.01$) were significantly more common among children with negative OFCs to eggs (Table 1). A negative peanut skin test ($p = 0.04$) and a diagnosis of asthma ($p = 0.03$) were significantly more common among children with negative peanut OFCs (Table 1). The age of the child, the duration of time since the last adverse reaction, and the severity of the initial adverse reaction to the food (including comparison between children with and without clinical adverse reaction [*i.e.*, sensitization only]) did not differ between children who had positive versus negative OFC to any of these foods.

Multivariate Analyses

For each food, variables from the univariate analyses with significance levels of $p \leq 0.1$ were included in logistic regression models (Table 2). For all foods, lower FSIgE levels were independently associated with increased likelihood of negative challenge. Higher total IgE level was associated with an increased likelihood of negative OFC to milk. Eating egg as an ingredient in baked goods was the factor most strongly associated with negative OFC to egg. Non-Caucasian race was associated with increased likelihood of negative OFC to egg and peanut. Overall, the milk and egg models had moderate power for identifying negative OFCs with areas under the ROC curves of 0.79 and 0.77, respectively, and the peanut model had a more modest area under the ROC curve of 0.66.

There was no difference in the outcome of the OFC based on the history of clinical reaction to the food (*i.e.*, clinical food allergy versus “sensitization only”; Table 1). However, to investigate whether the presence or absence of clinical reaction to the food affected the prediction models, we performed sensitivity analyses of the logistic regression models including only children with clinical food allergy (*i.e.*, excluding those with sensitization only). Although these analyses were limited by decreased statistical power for each model because of smaller sample sizes (data not shown), we found no meaningful change of the main effects in the models in these sensitivity analyses indicating that the inclusion of those with “sensitization only” did not alter the findings and reinforces that these children with FSIgE levels <2 kU/L for milk and egg and <5 kU/L for peanut are at risk for clinical reactions during OFC.

Proportion of Negative OFCs Using Factors Identified in Regression Models

To show the potential clinical usefulness of our models, we calculated the actual proportions of negative

Table 1 Demographics and clinical characteristics of study participants

	Milk OFC			Egg OFC			Peanut OFC		
	Positive (n = 32)	Negative (n = 44)	p Value	Positive (n = 98)	Negative (n = 72)	p Value	Positive (n = 72)	Negative (n = 126)	p Value
Age, mo (mean, SD)	44 (34)	46 (33)	0.8	50 (27)	53 (29)	0.49	69	68	0.73
Gender, male	23 (72%)	32 (73%)	0.93	71 (74%)	44 (61%)	0.12	46 (60%)	76 (64%)	0.62
Race, Caucasian	28 (87%)	34 (85%)	0.8	78* (88%)	45* (71%)	0.01	58* (94%)	96* (84%)	0.07
Time since last adverse reaction, mo (median [Q1, Q3])†	17 (10, 25)	21 (9, 33)	0.94	24 (13, 32)	25 (12, 39)	0.59	36 (22, 53)	35 (21, 52)	0.94
Eats the food as an ingredient	5 (16%)	13 (30%)	0.15	27 (28%)	44 (61%)	<0.01	0 (0%)	0 (0%)	1
Severity of adverse reaction#									
No clinical reaction	2 (6%)	5 (11%)	0.44	21 (21%)	18 (25%)	0.99	26 (36%)	49 (39%)	0.21
(sensitization only)									
One system	20 (62%)	27 (61%)		57 (58%)	36 (50%)		27 (37%)	59 (47%)	
Two systems	7 (22%)	12 (27%)		14 (14%)	15 (21%)		13 (18%)	14 (11%)	
Three systems	0 (0%)	0 (0%)		5 (5%)	2 (3%)		5 (7%)	2 (2%)	
Four systems	3 (9%)	0 (0%)		1 (1%)	1 (1%)		1 (1%)	2 (2%)	
Eczema in infancy	21 (68%)	26 (59%)	0.44	72 (74%)	48 (69%)	0.42	42 (61%)	70 (57%)	0.63
Current dx of eczema	18 (56%)	22 (50%)	0.59	56 (57%)	42 (59%)	0.79	28 (39%)	57 (45%)	0.39
Current dx of asthma	11 (34%)	20 (45%)	0.33	49 (50%)	42 (58%)	0.28	24 (33%)	62 (49%)	0.03
Current dx of allergic rhinitis	12 (37%)	22 (50%)	0.28	52 (53%)	40 (56%)	0.74	37 (51%)	78 (62%)	0.15
Current dx of other food allergies	19 (59%)	19 (43%)	0.16	54 (55%)	35 (49%)	0.4	30 (42%)	41 (33%)	0.20
FSIgE, kUa/L (mean, SD)	0.90 (0.5)	0.64 (0.5)	0.03	0.93 (0.6)	0.52 (0.5)	<0.01	0.76 (0.7)	0.57 (0.7)	0.07
Total IgE, IU/mL	148** (43, 196)	162** (36, 409)	0.02	111** (44, 259)	66** (26, 278)	0.9	87*** (34, 189)	75*** (32, 286)	0.16
(median[Q1,Q3])§									
Positive skin test	25* (93%)	35* (90%)	0.7	87 (96%)	55 (83%)	<0.01	62 (95%)	99 (85%)	0.04

Data presented as the number of children (%) in each category unless otherwise noted. The p value represents the results of the univariate analysis comparing these potential predictors among children who had positive vs negative OFC. Frequency of missing data is <10% for each variable unless otherwise noted: *11–20% missing data, **21–30% missing data, ***>30% missing data.

#Severity score was adapted from DuunGalein et al¹³. Severity of the adverse reaction is a reflection of the number of body systems that were involved in the initial adverse reaction to the food. No clinical reaction (sensitization only) serves as the reference value. Each of the other categories is compared with this reference value.

§Variable is not normally distributed: data presented as the median (Q1, Q3).

FSIgE = food-specific IgE; OFC = oral food challenge.

Table 2 Results of multivariate analyses using logistic regression models for the prediction of negative OFCs

Food	Predictor	β - estimate	Odds Ratio	Odds Ratio 95% CI
Milk	FSIgE*	−1.911	0.826	0.72–0.95
	Total IgE#	0.005	1.04	1.01–1.08
Egg	FSIgE*	−1.308	0.877	0.82–0.94
	Eat as ingredient in baked products	1.073	2.924	1.40–6.10
	Race (non-Caucasian) §	0.296	1.345	1.06–1.71
Peanut	FSIgE*	−0.512	0.950	0.90–0.99
	Race (non-Caucasian) §	0.337	1.401	1.03–1.91

Table represents the estimators, odds ratios, and confidence intervals for predictors that remained significant in multivariate analysis.

*Odds ratio was calculated per 0.1-U increase in FSIgE.

#Odds ratio was calculated per 10-U increase in total IgE.

§Compared with the indicator that is Caucasian.

FSIgE = food-specific IgE; OFC = oral food challenge.

OFC using all combinations of the significant factors for each model (Table 3). We identified combinations of factors that define subgroups of children that had higher proportions of negative OFCs, whereas different combinations of factors resulted in lower proportions of negative OFCs. For example, the proportion of negative egg OFCs among non-Caucasian children who had FSIgE \leq 0.36 kUa/L and ate baked goods with egg was 75%, while Caucasian children who had FSIgE $>$ 0.96 kUa/L and who do not eat baked goods with egg experienced negative egg OFCs only 12.9% of the time. Similar subgroups were identified in the milk and peanut models (Table 3).

DISCUSSION

The current food allergy guidelines suggest that performing OFCs, aimed to document tolerance to the food, once the FSIgE value is \leq 2 kUa/L to milk, egg, and peanut (or \leq 5 kUa/L for sensitization only to peanut) is appropriate because it is associated with \sim 50% likelihood of negative OFC.³ Our study confirmed these recommendations by showing that the proportions of negative OFCs while using these cutoffs were 58% to milk, 42% to egg, and 63% to peanut. Moreover, we showed that incorporating clinical and laboratory data into regression models and using FSIgE values in a continuous range rather than single cutoff value can identify subgroups of children who have increased likelihoods for negative OFCs. Overall, we identified combinations of factors that in our cohort resulted in proportions of negative OFCs of 83, 75, and 75% to milk, egg, and peanut, respectively.

Our models identified several independent factors associated with increased likelihoods of negative OFCs. We found that even within the range of FSIgE of \leq 2 kUa/L, lower levels of FSIgEs were associated with increased likelihoods of negative OFC to milk, egg, and peanut. Higher total IgE was associated with increased likelihood of negative milk OFCs. We do not fully understand the mechanism behind this finding, but similar (albeit not significant) trends were previously reported in statistical models that were designed to predict results of OFC to milk.¹³ Eating egg as an ingredient in baked goods was common among our egg-allergic children (42%) and was the factor most strongly associated with negative OFC to egg. This finding is consistent with recent data suggesting that, in a subset of egg-allergic children, ingestion of heated egg is well tolerated and might facilitate tolerance.^{17,18} In addition, although negative skin tests (egg and peanut) were significantly associated with negative OFCs in the univariate analyses, they were not significant in the regression models, likely because of collinearity of skin test results with FSIgE values.

We intentionally selected patients with FSIgE of \leq 2 kUa/L because these are the children defined by the current clinical recommendations as the most appropriate candidates for OFC aimed to document tolerance to food.³ Our goal was to maximize the proportion of negative OFCs within this group. A previous study¹³ reported negative OFCs among children with higher FSIgE values. DunnGalvin *et al.*¹³ sought to develop a model that might replace OFCs in diagnosing food allergy. Their models were developed retro-

Table 3 OFC outcomes based on clinical and laboratory parameters

OFCs to Milk:

FSIgE (kUa/L)*	Total IgE (IU/mL)*	Proportion (n) of Negative OFC to Milk
Below the median (FSIgE ≤ 0.53 kUa/L)	Above the median (total IgE > 153.6 IU/mL)	83.3% (12)
	Below the median (total IgE ≤ 153.6 IU/mL)	80.0% (15)
Above the median (FSIgE > 0.53 kUa/L)	Above the median (total IgE > 153.6 IU/mL)	57.1% (14)
	Below the median (total IgE ≤ 153.6 IU/mL)	33.3% (12)

OFCs to Egg:

FSIgE (kUa/L)	Race	Eats Baked Egg Products	Proportion (n) of Negative OFC to Egg
Lowest tertile (FSIgE ≤ 0.36 kUa/L)	Non-Caucasian	Yes	75.0% (4)
		No	66.7% (3)
	Caucasian	Yes	73.7% (19)
		No	58.3% (24)
Middle tertile (0.36 kUa/L $<$ FSIgE ≤ 0.96 kUa/L)	Non-Caucasian	Yes	71.4% (7)
		No	75.0% (4)
	Caucasian	Caucasian	44.4% (18)
		No	4.5% (22)
Highest tertile (FSIgE > 0.96 kUa/L)	Non-Caucasian	Yes	75.0% (4)
		No	28.6% (7)
	Caucasian	Yes	44.4% (9)
		No	12.9% (31)

OFCs to Peanut:

FSIgE (kUa/L)	Race	Proportion (n) of Negative OFC to Peanut
Lowest tertile (FSIgE ≤ 0.17 kUa/L)	Non-Caucasian	75% (8)
	Caucasian	77.5% (80)
Middle tertile (0.17 kUa/L $<$ FSIgE ≤ 0.65 kUa/L)	Non-Caucasian	100% (4)
	Caucasian	48% (25)
Highest tertile (FSIgE > 0.65 kUa/L)	Non-Caucasian	80.0% (10)
	Caucasian	44.6% (49)

*Ranges were defined based on medians and not tertiles because of relatively small sample size of the Milk OFCs
FSIgE = food-specific IgE; OFC = oral food challenge.

spectively and then validated in an independent cohort. These models addressed a different clinical question, namely establishing the diagnosis of food allergy. Thus, DunnGalvin's¹³ population included children with higher mean FSIgE and a wider range of FSIgE values. In contrast, the aim of our OFCs was mainly to document resolution of food allergy. As a result, our study population is confined to the lower end of the FSIgEs range. These major differences in aims and, subsequently, in study population are likely to explain why the main predictors in the DunnGalvin's model (e.g., severity scores of previous reaction and skin tests results) were not shown to be significant in our cohort. We suggest that the severity of clinical reaction at the initial event and positive skin test findings are infor-

mative in establishing a diagnosis of food allergy (as reported by DunnGalvin¹³), but may be less informative in a child already diagnosed with food allergy and presenting to investigate whether he/she developed resolution of food allergy.

Retrospective data collection is a limitation of our study. However, retrospective data collection was used in most previous studies aimed to predict outcomes of OFC,^{10,12,13} which were later validated in prospective independent cohorts.^{9,13} In addition, we took several measures to minimize bias in our study and to increase the validity of our findings. To minimize potential selection bias, we established clearly defined inclusion/exclusion criteria that assured that we identified the population of interest: children presenting for OFC

based on a predefined set of clinical and laboratory characteristics. To minimize potential measurement bias, data were collected by a trained research assistant using a predefined questionnaire. Finally, we did not perform double-blind placebo-controlled OFCs because graded OFCs are considered to be an adequate and cost-effective method in the clinical setting,^{3,4,19} and we took efforts to minimize potential measurement bias resulting from nonobjective symptoms during the challenge, as described in the Methods section. Moreover, to minimize potential false negative results of the graded challenge, each negative graded challenge was followed by an open consumption of a meal-sized portion of the food. However, a recent report²⁰ suggested that a small proportion of children who had a negative graded challenge may react to the food if the open challenge is performed a day after the graded challenge. It is not known from that report if similar findings will occur if a similar dose of food will be given at the same day after the graded challenge rather than a day later. While reactions to food on the days after negative challenge are not commonly reported, we did not directly assess for such reactions in our study.

In summary, we have confirmed that the currently recommended FSIgE cutoffs to guide the decision to perform OFC aiming to document resolution or allergy to milk, egg, and peanut³ result in rates of negative OFCs of ~50%. We identified food-specific clinical factors that were independently associated with greater likelihood of negative OFC and identified combinations of factors that were associated with increased likelihood of negative OFCs in our population. These findings will need to be validated in a different population and if confirmed, then clinicians will be able to use this information to better estimate the risk-to-benefit ratio of each challenge.

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